

# Development of the Aortic Baroreflex in Microgravity

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## ABSTRACT

Baroreceptors sense pressure in blood vessels and send this information to the brain. The primary baroreceptors are located in the main blood vessel leaving the heart (the aorta) and in the arteries in the neck (the carotid arteries). The brain uses information from the baroreceptors to determine whether blood pressure should be raised or lowered. These reflex responses are called baroreflexes.

Changing position within a gravity field (i.e., moving from lying to sitting or standing) powerfully stimulates the baroreflexes. In weightlessness, the amount of stimuli that the baroreflexes receive is dramatically reduced. If this reduction occurs when the pathways that control the baroreflexes are being formed, it is possible that either the structure or function of the baroreceptors may be permanently changed.

To study the effect of microgravity on structural and functional development of the aortic baroreflex system, we studied young rats (eight days old at launch) that flew on the Space Shuttle *Columbia* for 16 days. Six rats were studied on landing day; another six were studied after re-adapting to Earth's gravity for 30 days. On both landing day and 30 days after landing, we tested the sensitivity of the rats' baroreflex response. While the rats were anaesthetized, we recorded their arterial pressure, heart rate, and aortic nerve activity. After the tissues were preserved with perfusion fixation, we also examined the baroreflex structures.

On landing day, we found that, compared to the controls, the flight rats had:

- fewer unmyelinated nerve fibers in their aortic nerves
- lower baroreflex sensitivity
- significantly lower contraction ability and wall tension of the aorta
- a reduced number of smooth muscle cells in the aorta.

In the 30-day recovery group, the sensitivity of the baroreflex showed no difference between the flight rats and the control groups, although the unmyelinated fibers of the aortic nerve remained reduced in the flight rats.

The results show that spaceflight does affect the development of the aortic baroreflex. The sensitivity of the reflex may be suppressed; however, the function of the blood pressure control system can re-adapt to Earth's gravity if the rats return before maturation. The structural differences in the input pathway of the reflex (i.e., the reduction in nerve fibers) may remain permanently.

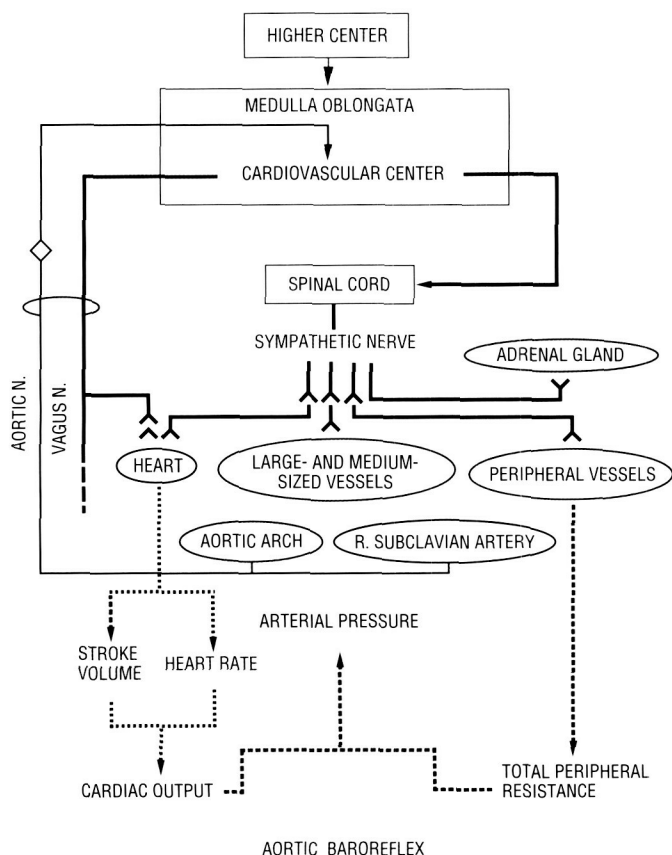
## INTRODUCTION

Gravity profoundly affects blood circulation. Without the blood pressure control system, our blood pressure would increase when we were lying down and decrease whenever we stood up. Fortunately, our pressure control system allows us to adjust rapidly to changes in position.

In weightlessness, the cardiovascular system does not have to adjust to changes in body position. If animals were to grow up in space and not be exposed to these stimuli, it is not known how their cardiovascular systems would develop. Animals that develop in microgravity would not experience the usual changes that gravity produces in the cardiovascular system, and this stimulation may be important for normal development. In our experiment, we studied the effect of microgravity on the development of an important part of the blood pressure control system (Gootman, 2000)—the aortic baroreflex.

The aortic baroreflex is a negative feedback mechanism that maintains blood pressure at a constant level by a reflex (Figure 1). In general, a reflex arc is composed of: (a) sensors, (b) afferent nerves that carry the sensory information to a control center, (c) a control center, (d) efferent nerves that carry the appropriate responses back to the tissues, and (e) effectors.

In the aortic baroreflex, the sensors are free endings of the *aortic nerve distributed in the outer and middle layers of the wall of the aortic arch and the right subclavian artery.*



**Figure 1.** Schematic representation of the aortic baroreflex system (see Text). N: nerve

The afferent nerves (carry signals to the brain) are the left and right aortic nerves. The control center is located in the medulla oblongata of the brain. The efferent nerves (carry signals from the brain) are both the sympathetic and parasympathetic nerves of the autonomic nervous system that distribute to the effectors—the heart and blood vessels. The sensory receptors and afferent fibers are stimulated by stretching the vessel's wall when blood flow increases and blood pressure is elevated. A decrease in blood pressure removes this stimulation. The control center in the brain stem is stimulated or inhibited by receiving this sensory information. The output from the center controls the output of the cardiac parasympathetic nerve (the vagus nerve) and of the sympathetic nerves that originate in the spinal cord and innervate both the blood vessels and the heart. These impulses return blood pressure to normal by affecting the heart's contractile force, the number of heartbeats per minute, and the diameter of blood vessels.

In rats, the baroreflex system grows and develops to maturity during the first eight to 12 weeks after birth. We have previously found the following facts about the development of the aortic baroreflex in the rabbit (Shimizu, 1990) and rat (Yamasaki, 1996):

1. The aortic nerve is composed of myelinated nerve fibers (myelin is a protective sheath on the nerve), which have a low threshold for excitation, and unmyelinated nerve fibers, which have a high threshold and irregular discharges.
2. After birth, the myelinated fibers continue to increase in number, myelin thickness, and axon diameter.
3. In the rabbit, the increase in the number of myelinated fibers correlates linearly with age-related increases in mean arterial blood pressure.
4. The response of the aortic nerve to increases in arterial pressure is smaller in the young rat and rabbit than in the mature rat and rabbit.
5. The bradycardiac response of the aortic baroreflex (i.e., decrease in the heart rate in response to an increase of blood pressure) is smaller in the young rabbit than in the mature rabbit.
6. At around eight to 12 weeks of age, the composition of the aortic nerve in both rat and rabbit and the bradycardiac response in the rabbit become the adult type.

Ground-based simulations of weightlessness have shown changes in the aortic baroreflex. To simulate the headward shift of body fluid that occurs when a human enters space (Charles, 1994), we used head-down tilt (HDT) studies. With HDT, blood flow and arterial pressure increase in the ascending aorta. When rabbits aged three to four weeks were raised in a special cage where the animals experienced HDT for 34–36 days, the number of unmyelinated fibers of the aortic nerve was significantly reduced compared with that of the control groups. The proportion of unmyelinated fibers to all nerve fibers in the aortic nerve was smaller in the HDT group than in the control groups,

although there was no difference in the number of myelinated fibers among three groups. Aortic nerve activity and the bradycardiac response of the aortic baroreflex were less in the HDT group than in the control groups (Yamasaki, 2002).

We proposed the following hypotheses based on these ground-based experiments. In the developing rat exposed to microgravity in space:

1. the mechanical behavior of the baroreceptor region of the aortic arch and its branches would be modified due to the redistribution of blood flow that occurs under conditions of microgravity,
2. the composition of the aortic nerve would be changed,
3. there would be a modification of the baroreceptor reflex function that would affect the nervous control of blood circulation.

The purpose of the present space experiment was to substantiate our hypotheses by observing and analyzing the effect of microgravity on baroreflex responsiveness, the quantity of aortic nerve fibers, and the structure and function of the various tissues related to the baroreflex.

## METHODS

### General Procedure

Sprague-Dawley rats, aged eight days, were flown on the Space Shuttle *Columbia* for 16 days. Two types of control groups were prepared on the ground. One was the asynchronous ground control (AGC) group, where the rats were raised in flight-like cages, and the other was the vivarium (VIV) control group, where the rats were raised in commercial cages.

### Animal Care and Welfare

The experiments were performed according to the guidelines of the NASA-Ames Research Center (ARC) *Animal Care and Use Handbook* and were reviewed by the Institutional Animal Care and Use Committee (IACUC) at NASA-ARC and the NASA-Kennedy Space Center (KSC). We also followed the Guidelines for Animal Experiments at Fukushima Medical University, and the Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences declared by the Physiological Society of Japan.

### Assignment and Anesthesia of the Animals

On landing day (recovery day zero or R+0), six flight rats aged 24 days were studied and six more rats were reserved for 30 more days (recovery day 30 or R+30) on the ground. Anesthesia was provided using a 25% urethane solution (1.2 to 1.5g/kg in female rats, 1.5 to 2.0g/kg in male rats) injected into the intraperitoneal cavity. The dose of urethane was determined according to the body weight and sex of each rat on the basis of our previous examinations (unpublished data). The control groups were treated using the same protocol as the flight groups.

## Functional Examinations

*Tests for baroreflex responsiveness and afferent sensitivity* – Arterial pressure, heart rate, aortic nerve activity, and respiratory movements were measured under anesthesia. These parameters were recorded simultaneously on magnetic tape, computer disk, and penrecorder chart; and changes in these parameters accompanying the changes in blood pressure were observed. Arterial pressure was increased or decreased by the venous injection of phenylephrine or sodium nitroprusside, respectively. Arterial baroreflex responsiveness was expressed by dividing the percentage change in heart rate by the percentage change in mean blood pressure (percent change of heart rate ( $\Delta HR\%$ )/percent change of mean blood pressure ( $\Delta MBP\%$ )). Sensitivity of the aortic nerve was determined by calculating the percentage change in aortic nerve activity for a change in mean blood pressure (percent change of the aortic nerve activity ( $\Delta ANA\%$ )/percent change of mean blood pressure ( $\Delta MBP\%$ )).

*Tests for mechanical properties of the aortic wall* – The mechanical properties of the thoracic aorta wall were examined in six rats prior to fixation. The aorta was divided into two portions. One portion was gradually frozen to  $-70^{\circ}\text{C}$  and transported to Japan to test its mechanical properties (elasticity, extensibility, etc.) (Patel, 1972). The other portion was used for contraction-relaxation tests at the landing site.

*Tensile tests* – To examine the mechanical properties of the aortic wall, we did a specific tensile test with a tensile testing instrument (TDM-30J, Miebec, Inc., Japan). This examination quantifies the elasticity, plasticity, and extensibility of the vessel wall.

*Contraction-relaxation test* – The lower half of the thoracic aorta was divided into three to four ring-shaped samples (approximately 2.0–3.0 mm in width and 0.5–1.0 mm in diameter). The contraction and relaxation were elicited by application of drugs that change excitation of the smooth muscle in the vessel wall; i.e., phenylephrine for producing contraction and acetylcholine for producing relaxation. We also studied the role of the cells lining the inside of the vessel by applying L-NAME to inhibit production of nitric oxide in the endothelium cell or by removing the endothelium mechanically. These experiments were performed under indomethacin application to inhibit production of vasoactive prostanoids, which are also produced by endothelium cells.

## Histological Examinations

*Fixation and dissection of tissues* – After the baroreflex tests, tissues were preserved with chemical fixatives. A modified Kalnowski solution containing 1% paraformaldehyde and 1% glutaraldehyde was used.

*Electron microscopic examination of the aortic nerve* – Electron microscopic montages of transverse sections of the aortic nerve trunks were printed out at 13,400 times magnification. The unmyelinated and myelinated nerve fibers were counted on the montages. The long and short axes (a and b) of the nerve fibers and the myelin thickness (T) were measured with calipers.

*Examination of gene expression in various tissues* – Different genes in the tissues can be turned on or expressed in response to various stimuli, and this can produce important growth factors and proteins. In our study, we analyzed the expression of epidermal growth factor (EGF), proliferating cell nuclear antigen (PCNA), lysozyme, and vitamin D<sub>3</sub> receptor (VDR). Total RNA was isolated from the liver, spleen, intestine, and thymus, and RNA concentration was quantified by spectrophotometry.

*Statistical analysis* – The data were statistically analyzed with one-way analysis of variance (ANOVA) or non-paired student's t-test and followed by Scheff's F test or Bonferroni/Dunn test. The values were expressed as mean±SD, and statistical significance was set at p<0.05.

## RESULTS

### General Observations

The flight rats walked with difficulty after landing. Approximately four hours after landing at NASA-KSC, they moved slowly and squatted frequently. By about six hours after landing, they were able to move quickly and smoothly. Initially, the rats' fur was slightly brown and wet. In most flight rats, the tips of the tails were slightly necrotic. The body weight of the flight rats on R+0 was reduced compared to the ground control groups. An average value of body weight (n=6) was 53.4±4.8g in flight, 78.9±7.1g in AGC, and 84.3±4.2g in VIV. The animals in the recovery group (R+30) in flight grew well and did not differ in weight from the AGC and VIV groups (average body weight (n=6) was 214.2±46.0g in flight, 203.0±13.4g in AGC, and 221.1±9.3g in VIV).

### Functional Observations

*Basal blood pressure, heart rate, and respiratory movements* – Before the baroreflex tests, we measured blood pressure, heart rate, and respiratory movements under anesthesia (Figure 2). Among the six rats in the flight group used on R+0, two animals showed very low blood pressure (less than 40 mmHg of mean blood pressure (MBP)) and had no response to the drugs. The body weight of these rats was 47.4g and 47.7g, which was markedly lighter than the body weight of the other four rats (53.1±6.1g). Their heart rates were 378 beats per minute (bpm) and 361 bpm, which was less than the heart rate in the other four rats (462–520 bpm). Consequently, we did not record aortic nerve activity on these two rats, and we excluded these two rats from the analysis of the cardiovascular variables.

The baseline values for heart rate, blood pressure, and respiratory rate are shown in Table 1. On landing day, blood pressure in the flight rats was reduced compared to both in AGC and VIV, although this was statistically significant only between the flight rats and AGC. On R+30 there were no significant differences between the flight rats and the control groups. Blood pressure in the flight rats on R+30 was significantly higher than that measured on R+0.

On landing day, heart rates in the flight rats were higher than in each control group, although this was statistically significant only between the flight rats and VIV controls. On R+30, all groups showed lower heart rates than those on R+0, but there was no significant difference between the groups on R+30.

Respiratory rate decreased between landing day and R+30, but there was no difference among three groups at R+30.

**Table 1.** Baseline values for heart rate, blood pressure, and respiratory rate on landing day and 30 days after landing.

	Landing Day	30 days postlanding
<b>HR Flight</b>	492±24	343±35
<b>HR AGC</b>	452±33	386±32
<b>HR VIV</b>	428±41	415±36
<b>RR Flight</b>	122±16	104±32
<b>RR AGC</b>	133±7	105±17
<b>RR VIV</b>	119±8	106±13
<b>MBP Flight</b>	80.1±3.6	102.6±17.9
<b>MBP AGC</b>	96.9±5.7	98±15.2
<b>MBP VIV</b>	89.5±6.8	107.6±10.6
<b>SBP Flight</b>	90.4±10.3	120.8±14.5
<b>SBP AGC</b>	106.1±4.9	114.8±10.5
<b>SBP VIV</b>	99.6±9.9	121.1±9.3
<b>DBP Flight</b>	67.5±4.0	83.5±18.3
<b>DBP AGC</b>	84.5±6.7	98.0±15.2
<b>DBP VIV</b>	79.7±7.1	91.0±12.0

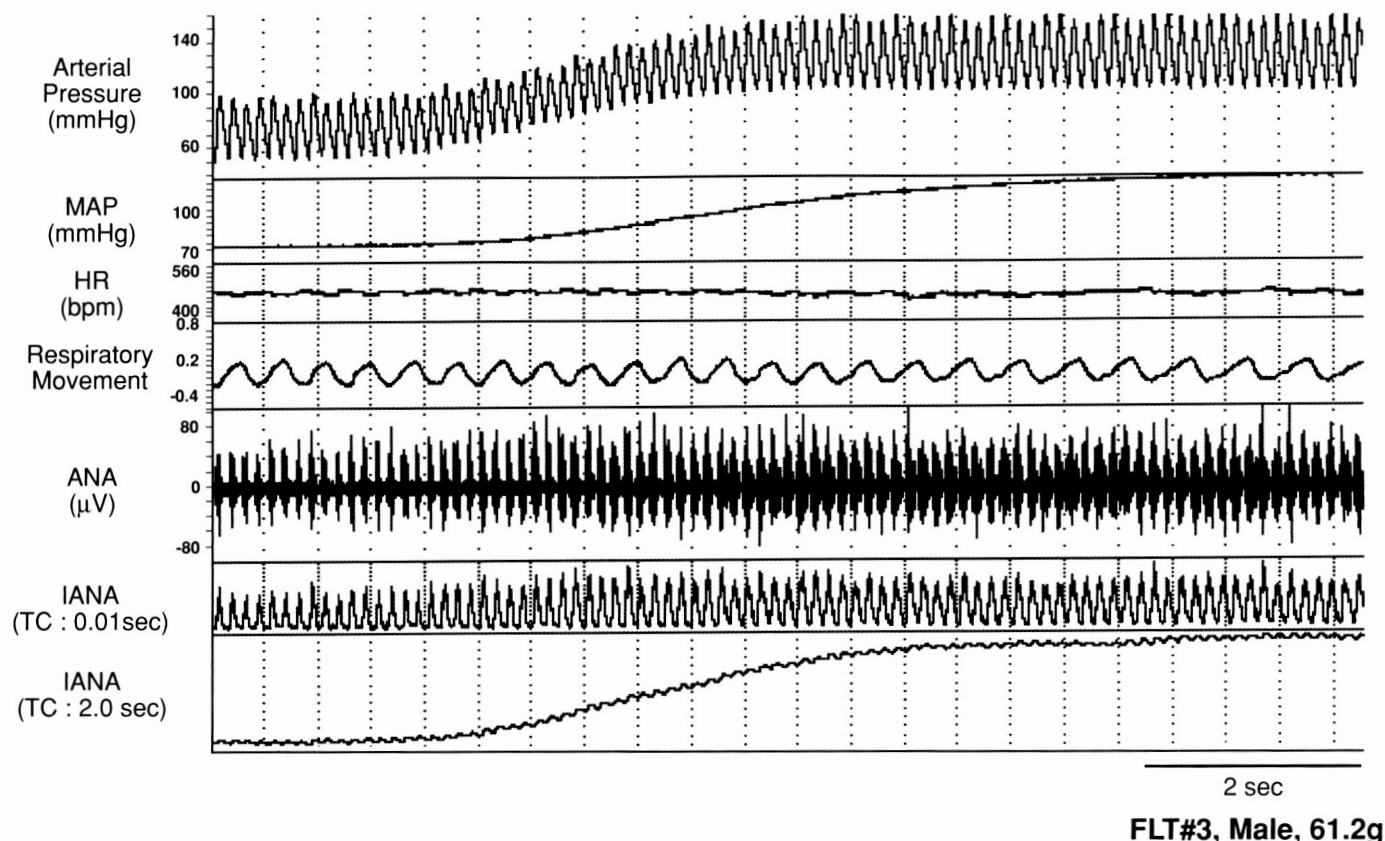
HR = heart rate (bpm), RR = respiratory rate (rpm), MBP = mean blood pressure (mmHg), SBP = systolic blood pressure (mmHg), DBP = diastolic blood pressure (mmHg). Flight = flight rats, AGC = asynchronous ground control group, VIV = vivarium control group.

*Responses of arterial baroreflex* – On R+0, the maximum decrease in heart rate produced by phenylephrine was less in the flight animals than in either control group. Also, the increase in blood pressure for a given dose of phenylephrine was significantly lower for flight rats. These differences were gone by R+30.

The index of baroreceptor reflex sensitivity ( $\Delta\text{HR}\%/\Delta\text{MBP}\%$ ) was calculated from the percentage changes from baseline values in mean blood pressure and heart rate. On R+0, the flight rats showed the lowest value ( $-0.19\pm0.08$ ). There was a significant difference between flight and AGC groups ( $-0.47\pm0.14$ ). When baroreflex sensitivity was calculated using absolute values rather than percentage change, no significant differences were found among all groups. The flight rats, however, showed the lowest values. The baroreflex sensitivity index was widely dispersed on R+30, and no significant differences were observed among the three groups (Figure 3A).

*Sensitivity of the aortic nerve as the input pathway in the aortic baroreflex* – Figure 2 shows typical responses of aortic nerve activity accompanying blood pressure changes due to phenylephrine injection. These data were obtained at R+0 in flight rats.

In all the flight rats, the integrated aortic nerve activity (IANA) showed qualitatively similar responses to those



FLT#3, Male, 61.2g

**Figure 2.** Responses of physiological parameters to the injection of phenylephrine recorded in a flight rat on landing day. MAP: mean aortic pressure (mmHg) HR: heart rate (bpm) ANA: aortic nerve activity ( $\mu\text{V}$ ) IANA: integrated aortic nerve activity ( $\mu\text{V}$ ) TC: time constant

observed in the ground controls; i.e., when blood pressure increased, IANA also increased, and when mean aortic pressure (MAP) decreased, IANA also decreased. However, the sigmoid curves of the MAP-IANA relationship in the flight rats shifted to the left compared to those of the VIV and AGC groups.

The afferent sensitivity of the aortic baroreceptor reflex in response to an increase of blood pressure on R+0 was lower in flight rats than in the controls. Two flight rats showed the lowest sensitivity (1.76 and 1.54) among all the rats tested (range 1.90–4.40) (Figure 3B), although the differences between each group were not statistically different. The afferent sensitivity on R+30 in the flight rats was significantly higher than that on R+0. No significant differences in the afferent sensitivity between the groups on R+30 were observed.

### Functional properties of the thoracic aorta

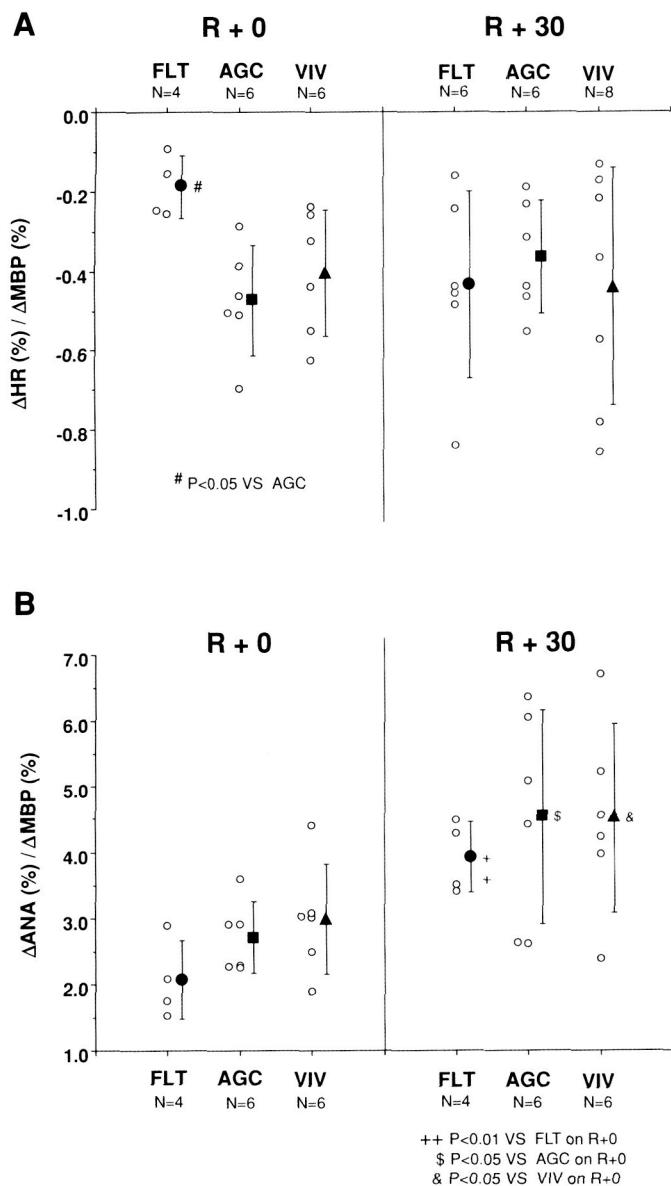
**Mechanical characteristics** – The tension produced by strain in the flight rats was significantly smaller than that in either the AGC or VIV groups (Figure 4A). The contour of the stress-strain curve derived from the corresponding tension-strain curve was almost similar among the three groups. The elastic moduli and the relaxation strength showed no significant difference among the three groups. Plastic deformation of the strip of the aortic wall ( $0.1 \pm 0.01 \text{ mm}$  : mean  $\pm$  SE) was observed in all samples in the flight group five minutes after the stress-strain test. It was not observed at all in the control groups.

**Vasoconstriction and vasorelaxation** – Phenylephrine caused dose-dependent contraction in the rings of the aorta. The sensitivity of the aortic wall with endothelium to phenylephrine ( $10^{-9} \text{ M}$  to  $3 \times 10^{-6} \text{ M}$ ), as a percent of the maximal response, averaged 6.4 for the three flight rats tested. This was smaller than the sensitivity in AGC ( $7.3 \pm 0.1$ ) and in VIV ( $7.1 \pm 0.1$ ), although we could not evaluate this statistically because some aortic rings in the flight group did not respond to the drugs. The maximum contraction in response to phenylephrine in the AGC and VIV groups was stronger than that for the flight group. Even in the presence of L-NAME, these curves showed similar relationships to the results of the above test (Figure 4B).

Acetylcholine ( $10^{-3} \text{ M}$  to  $3 \times 10^{-6} \text{ M}$ ) caused dose-dependent relaxation in the aorta rings with endothelium, and the relaxation showed no difference among the flight, AGC, and VIV groups. The relaxation was almost abolished in both situations of application of L-NAME ( $3 \times 10^{-4} \text{ M}$ ) to the ring with endothelium and the ring without endothelium.

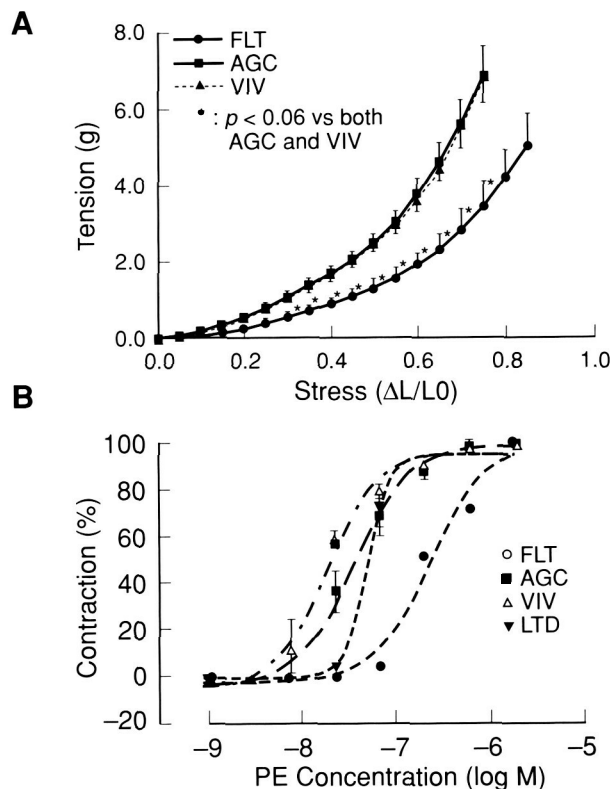
### Histological Observations

**Fine structure of the aortic nerve** – The aortic nerve samples available for electron microscopic analysis were extremely limited because of structural and technical problems (Figures 5A and 6). Careful examination of high-magnification montages of the transverse section in the left aortic nerves in five rats in each



**Figure 3.** Sensitivity of the baroreflex (A) and the aortic nerve. (B)  $\Delta MBP\%$ ,  $\Delta HR\%$  and  $\Delta ANA\%$ : maximum percent changes of mean blood pressure, heart rate, and integrated aortic nerve activity calculated with a time constant of 2.0 seconds in three experimental groups on the landing day (R+0) and on the 30th day of the recovery (R+30).

group at R+0 revealed that the number of unmyelinated fibers and the ratio of unmyelinated fibers to all fibers in aortic nerve fascicle were significantly less in the flight rats ( $139 \pm 37$ ,  $70.0 \pm 3.3\%$ ) than those in either AGC ( $207 \pm 36$ ,  $77.6 \pm 4.8\%$ ) or VIV ( $283 \pm 121$ ,  $75.2 \pm 9.9\%$ ) rats. There were no significant differences in the number of myelinated fibers among the three groups. The axon diameter ( $1.44 \pm 0.18 \mu m$  in flight,  $1.3 \pm 0.24 \mu m$  in AGC, and  $1.43 \pm 0.19 \mu m$  in VIV) and thickness ( $0.27 \pm 0.03 \mu m$  in flight,  $0.26 \pm 0.04 \mu m$  in AGC, and  $0.26 \pm 0.02 \mu m$  in VIV) of myelin in each aortic nerve showed no significant difference among the three groups.



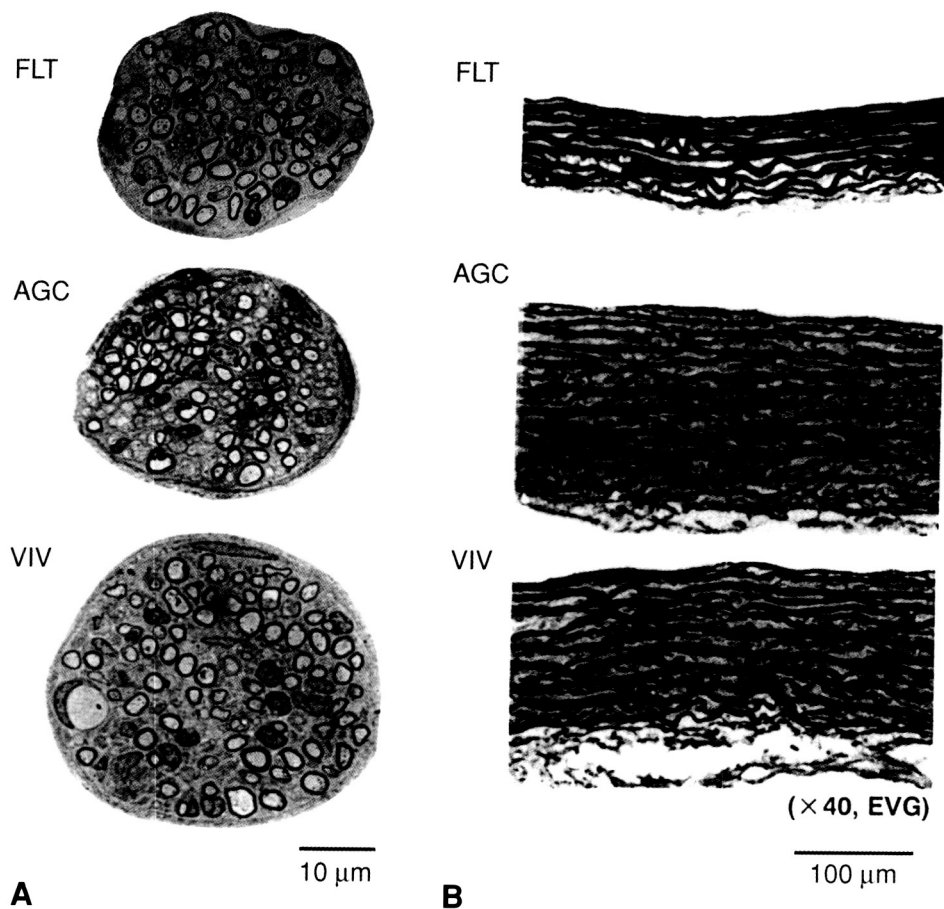
**Figure 4.** Tension production against stress and contraction elicited by phenylephrine in the wall of the thoracic aorta. FLT: flight group, AGC: asynchronous control group, VIV: vivarium control group, LTD: feeding-limited nursing group

On R+30 groups, the number of unmyelinated fibers was  $130 \pm 71$  in flight ( $n=4$ ),  $290 \pm 127$  in AGC ( $n=5$ ), and  $255 \pm 135$  in VIV ( $n=3$ ); and the ratio of unmyelinated fibers to all fibers was  $64.7 \pm 7.7\%$ ,  $77.3 \pm 6.1\%$ , and  $72.3 \pm 10.0\%$ , respectively. Both the number of aortic unmyelinated fibers and the ratio of myelinated to unmyelinated to all fibers remained significantly reduced in the flight rats at R+30.

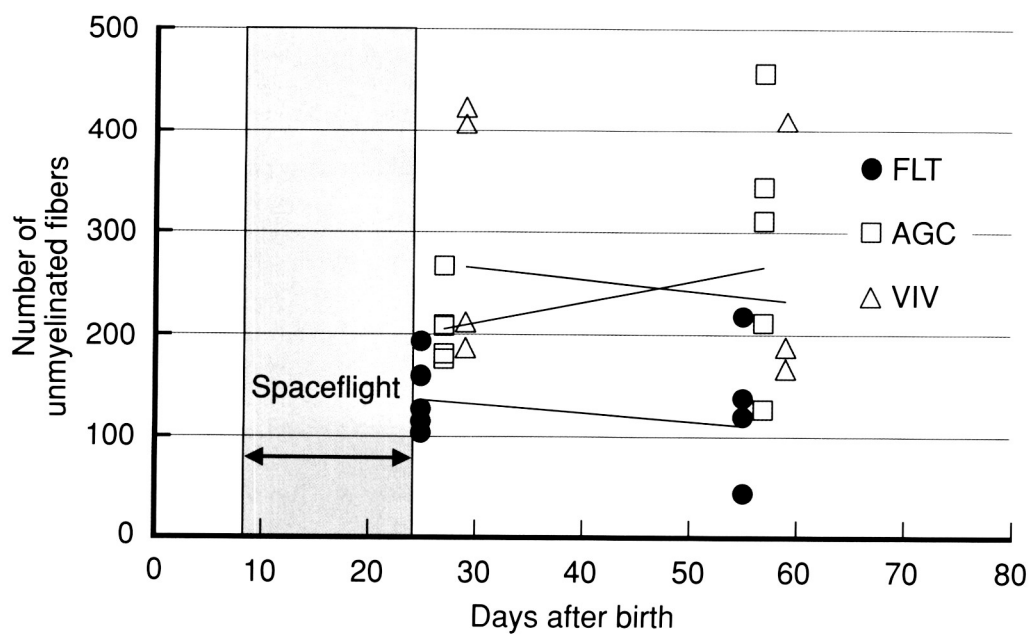
*Light microscopic observation of the aortic wall and the intestinal epithelium* – The thickness of the aortic wall in the flight rats was about 70% of that in the AGC and VIV rats (Figure 5B). The amount of smooth muscle cells was significantly less in the flight group. There were no significant differences among the three groups in amount of elastin and collagen fibers. The length of the crypt and Paneth cells in the small intestinal epithelium, which are important structures for digestion and absorption of nutrients, was not different among three groups.

*Relations of functional and structural parameters to the body weight* – The body weight of the flight rats four hours after landing was about 65% that of the AGC and VIV groups. To determine whether some of the changes we noted could be due to differences in body weight, we examined the correlation between the parameters we measured and the body weight in each group. There were no correlations between the parameters examined and the body weight, except for a relationship between mean blood pressure and body weight in the AGC group of R+30 recovery rats.

**Figure 5.** Electron microscopic photos of cross-sections of the aortic nerve (A) and light microscopic photos of the circumferential sections of the thoracic aorta (B).



**Figure 6.** Numbers of unmyelinated fibers of the left aortic nerve counted on landing day (R+0, age 24 days) and the 30th day of recovery (R+30, age 54 days). There were five in each group on R+0, and four in the flight group, five in the AGC group, and three in the VIV group on R+30.



*Gene expression of various organs* – Expression of VDR in the small intestine did not differ between the flight and ground control rats. Expression of platelet-derived growth factor (PDGF-b), which promotes the proliferation of vascular smooth muscle cells, and nerve growth factor (NGF 1B), which affects the growth and maintenance of nerve cells, was very low in the spleen of the flight rats.

## DISCUSSION

The results of our space experiments clearly demonstrated the following changes in the flight rats compared to ground controls:

- In the aortic nerve, the number of unmyelinated fibers (the high-threshold and irregularly discharging nerve fibers) was reduced, although the number and myelin thickness of myelinated fibers (the low-threshold and phasic firing nerve fibers) showed no difference from the controls.
- The sensitivity of both the reflex and the afferent nerve in the aortic baroreflex was reduced.
- The aortic wall also showed significant changes in structure and function. The wall thickness was thin with fewer smooth muscle cells present.
- The tension development against a strain and contraction force produced by a constricting drug (phenylephrine) was weak.

These findings support our hypotheses that microgravity affects the development of the aortic baroreflex. This provides a new understanding of the effect of gravity on nervous system development.

The experiment did have some limitations. The body weights of the flight rats were low compared to the body weights of ground control rats. This raises the question of whether the low body weight was caused by malnutrition (e.g., difficulties of nursing, malabsorption of nutrients, or changes in feeding behavior of the mothers), which influenced the results. The structural and functional differences observed in the flight rats might be due to malnutrition rather than weightlessness. There was, however, no correlation between the cardiovascular parameters we measured and the body weight at the same age in all experimental groups. Histological study and gene expression examinations of the small intestinal epithelium also showed that the epithelial structure of the small intestine developed normally for the absorption of nutrients (including calcium). The weight of the small intestinal tract and liver in the flight rats was not different from that in the controls. Furthermore, the myelination of the aortic nerve was quite normal. While it is reported that myelination is inhibited in malnutrition (Krigman, 1976), in a group of rats that was raised by feeding-limited nursing and that had a low body weight comparable to the 24-day-old rats in the flight group at the same age, the contraction properties of the aorta produced by application of phenylephrine showed no difference from the

control rats. Summarizing this evidence, the changes found in the flight rats are most likely not a consequence of malnutrition but rather are due to the space environment.

The study also provided important information on the re-adaptation back to one-G. The functional examination in the flight rats on R+0 started about six hours after landing and lasted for almost 12 hours. When the flight rats were inspected approximately three hours after landing, their behavior was similar to that observed under hypergravity conditions produced during parabolic flight. The rats gradually were able to move actively, and their walking behavior re-adapted to the ground within three to six hours after landing. In our experiments, the attenuation of the aortic baroreflex was still observed in rats that were tested on R+0 more than 10 hours after landing. From these observations, it appears that the regulation of the cardiovascular system seems not to re-adapt rapidly to the ground, and this could be due to structural changes that develop in space. Therefore, the time consumed before we performed the functional tests in this series of experiments on R+0 did not seriously affect the results obtained.

Based on these data, we propose the following mechanism for the changes observed in the flight rats. Following launch, body fluid redistributes and blood vessels located above the heart should receive more blood as compared to one-G. This increases the amount of blood the heart pumps, which increases blood flow in the ascending aorta, aortic arch, and arteries that perfuse the head. This elevates blood pressure in these vessels and expands these vessels' walls at the same time. The stretch of the aortic, subclavian, and carotid arteries excites the baroreceptors and elicits the baroreflex. As a result of the baroreflex, elevation of blood pressure is suppressed by relaxation of peripheral vessels and a slowing of the cardiac rhythm, thereby decreasing overall blood flow. These incidents have been partially demonstrated by us and others using HDT and parabolic flight methods (Shimizu, 1992; Yamasaki, 2002). The puffy face, nasal congestion, thickening of the eyelids, and reduction of leg girth reported by astronauts during real spaceflight have also demonstrated these effects (Charles, 1994).

If the stay in space continues, these acute phenomena become more stable, and the increase in body fluid and muscle cells that should occur during development slows down compared to what would occur in one-G. Not only the antigravity muscles but also other skeletal muscles work less and so are smaller. As a result, the body remains small-sized; i.e., a light body weight as compared to the ground controls of the same age. In space, blood is provided to every portion of the body with a constant pressure gradient. The distribution of blood flow may be affected more in space by the control of vessels to particular organs rather than by the increase of total blood flow in the aorta (Rowell, 1993). Active contraction of the aortic wall during the filling period of the heart is not essential. The absolute value of cardiac output (the amount of blood the heart pumps per minute) also becomes smaller compared to one-G because of a decrease in total body fluid. As a result, episodes elevating blood pressure in space are reduced as compared to on Earth. Therefore, the growth of the muscular component of the aortic wall is slower, which suppresses the development of contraction forces. Fewer

afferent nerve fibers are needed to respond to high blood pressure. Baroreflex sensitivity to blood pressure changes at high pressure levels is also reduced. This suppression of the baroreflex may be due to the structural properties of the afferent pathway (the aortic nerve) and effector organs (vessels). Also, it could be due partly to the effects of microgravity on the cardiovascular control center or on efferent pathways of the baroreflex.

After the growing rat returns to Earth from space, the function of the baroreflex system to control blood pressure can develop normally and adapt to the one-G Earth environment—if the rat returns while it is still developing. There is a possibility, however, that structural differences in the afferent pathway (aortic nerve) may remain permanently.

In conclusion, the space environment affects the development of the aortic baroreflex system and the regulation of blood circulation.

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